

## **REMARKS**

Applicants request entry of this amendment and reconsideration of the rejection of the claims.

Applicants have cancelled claims 14-21, 23-29, and 32-34 without prejudice or disclaimer. These claims have been cancelled as a result of a restriction requirement. Applicants request clarification concerning claim 20. The Examiner indicated claim 20 was pending, but claim 20 was not in the group I claims previously identified by the Examiner in the restriction requirement. Applicants believe that claim 22 should be pending and claim 20 withdrawn from consideration. Applicants have cancelled claim 20 and request the Examiner reinstate claim 22.

Applicants have amended claims 2-3, 5, 10-11, 13, 22, 30 and 31. Applicants submit the amendments are supported throughout the specification including at page 9, line 24 to page 10, line 15; page 7, lines 7-10; page 18, lines 13-27; and page 45, lines 10 to page 46, line 24.

Applicant present new claims 35-51 which are generally patterned after the original claims and are supported throughout the specification including at page 5, lines 1-6; page 9, line 24 to page 10, line 15; and page 50, line 6 to page 52, line 4.

Applicants submit the amendments to the claims and the new claims do not raise any issues of new matter.

## **In the Figures**

Applicants are hereby submitting a corrected Figure 7. Applicants note that the amino acid sequence of human thrombopoietin was known to those of skill in the art, for example, at GenBank Accession No. P40255 (copy attached). Applicants have not changed the amino acid sequence but have changed the numbering of the amino acid sequence to reflect the presence of the leader sequence at amino acid positions 1-21. The presence of the leader sequence was known to those of skill in the art, and therefore, Applicants submit that this correction in amino acid numbering is the correction of an obvious error.

### **Information Disclosure Statement**

Applicants note that the Information Disclosure Statement received at Tech Center on June 28, 2002 was not completely initialed. Applicants note the Muto et al. reference was not initialed. Applicants request that the Examiner consider the reference and return an initialed Form 1449 to Applicants.

### **35 U.S.C. § 112**

The Examiner objected to claim 31 as being of improper dependent form. Applicants submit the amendment to claim 31 obviates the objection and respectfully request withdrawal of the objection on this basis.

The Examiner has also rejected claims 1-13, 22, 30 and 31 under 35 U.S.C. § 112, second paragraph. Applicants have amended claims 2, 3, 5, 10, 11, 13, 22 and 30 to clarify the subject matter of the claims. Applicants submit the amendments to these claims address most of the Examiner's rejections.

With respect to the rejection of claim 12, Applicants respectfully traverse. Applicants direct the Examiner's attention to the definition of therapeutic in the specification at page 8, lines 6-15. Applicants submit that one of skill in the art reading the specification would know the meaning of the term therapeutic activity.

With respect to the rejection of claim 30, Applicants respectfully traverse. Applicants direct the Examiner's attention to the definition of immune response in the specification at page 7, lines 16-30. Applicants submit that one of skill in the art reading the specification would know the meaning of the term reducing an immune response.

Applicants, therefore, respectfully request withdrawal of the 35 U.S.C. § 112, second paragraph rejections.

### **35 U.S.C. § 103**

The Examiner has rejected claims 1-6, 8-13, 22, 30 and 31 as being unpatentable over Lovborg et al. (WO 92/10755) in view of Estell et al. WO 99/53038. Applicants respectfully traverse the rejection.

To establish a prima facie case of obviousness, three basic criteria must be met, namely: 1) the references when combined must teach or suggest all of the claim limitations; 2) suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings; and 3) a reasonable expectation of success. MPEP § 2142. Applicants argue that all of these requirements have not been met because in the least, because Lovborg et al. and Estell et al. do not teach all of the elements of the claimed invention.

Applicants' invention is directed to identifying at least one immunodominant epitope in a polypeptide using an antibody or population of antibodies from a naïve human or animal or population thereof, and modifying the immunodominant epitope to reduce an immune response to the polypeptide while retaining a substantial therapeutic activity of the polypeptide.

The Lovborg et al. reference is directed to a method for identifying epitopes in a protease molecule using antibodies from immunized animals. The Lovborg et al. reference does not teach or suggest that antibodies from naïve humans or animals are present and could be used to identify epitopes on polypeptides.

The deficiency of the Lovborg et al. reference is not remedied by reference to Estell et al. Estell et al. is directed to identifying T cell epitopes in a bacterial protease using naïve T cells. The reactivity of naïve T cells with the bacterial protease only indicates that upon exposure to the polypeptide, T cells can react to initiate a variety of immune responses. The Estell et al. reference does not teach or suggest that antibodies to polypeptides are present in a naïve human or animal in sufficient quantities to be useful to identify immunodominant epitopes. One of skill in the art would not have expected such antibodies to be present. It was surprising that antibodies to the polypeptide were found in humans that were not known to have been treated with the polypeptide.

With respect to claims 2, 3 and 22, Applicants respectfully submit that neither of the cited references teach or suggest using a polypeptide that has at least 80% sequence identity to a endogenous polypeptide in a human or animal. Both references are directed to heterologous polypeptides such as bacterial proteases. Applicants submit that it was unexpected that antibodies to an endogenous polypeptide in a human or animal could be formed. It was thought that immune responses were not typically generated to endogenous or self polypeptides. In fact, the Estell et al. reference teaches that to reduce the allergenic potential of the protein of interest the T cell epitope

of the protein is modified by substituting the amino acids of the bacterial protease with those of human protease. Estell indicates that as the bacterial protein is modified to more closely resemble the human protein in the T cell epitope, the immune response to the protease in humans is expected to be reduced. (See page 5 lines 4-18 and page 9, lines 13-34 of Estell et al.) The Estell et al. reference teaches away from applicants claimed invention because the reference suggests that an human immune response to an endogenous human protein would be expected to be reduced or not present. In contrast, applicants have found that antibodies to endogenous or self polypeptides are formed and that immunogenicity of endogenous or self proteins can be modified to reduce immune response to such polypeptides.

In summary, Applicants submit that the cited references do not make claims 1-6, 8-13, 22, 30 and 31 obvious because neither of the cited references teach or suggest that antibodies to polypeptides are present in a naïve human or animal and can be used to identify an immunodominant epitope. In addition, with respect to claims 2, 3 and 22, the references do not teach or suggest a method of identifying at least one immunodominant epitope in a polypeptide that has at least 80% amino acid sequence identity to an endogenous polypeptide. Thus, Applicants respectfully request withdrawal of the rejection on this basis.

The Examiner rejected claim 7 under 35 U.S.C. § 103 as being unpatentable over Lovborg et al. (WO 92/10755) in view of Estell et al. (WO 99/53038) and further in view of Garrity et al. (U.S. Patent No. 5,585,250). Applicants respectfully traverse the rejection.

Claim 7 is directed to a method of modifying a polypeptide comprising modifying at least one amino acid in an immunodominant epitope by N-glycosylation or N-pegylation. The immunodominant epitope is identified using an antibody or population of antibodies from a naïve human or animal.

As discussed previously, neither the Lovborg et al. or Estell et al. teach or suggest the presence or use of naïve antibodies to identify an immunodominant epitope. The deficiencies of these references is not remedied by Garrity et al. Garrity et al. describes immunodampening an epitope by introduction of N-linked carbohydrate residues. This reference does not teach or suggest using an antibody or population of antibodies from a naïve human or animal and, therefore, does not make obvious the claimed invention. Applicants respectfully request withdrawal of the rejection on this basis.

The Examiner also rejected claims 1-11, 22, 30 and 31 under 35 U.S.C. § 103 as unpatentable over Lovborg et al. in view of Estell et al., further in view of Garrity et al. and Bartley et al. (U.S. Patent No. 5,795,569). Applicants respectfully traverse the rejection.

As discussed previously, the Lovborg et al., Estell et al., and the Garrity et al. references do not teach or suggest the presence or use of antibody or population of antibodies obtained from a naïve human or animal. The deficiencies of these references are not remedied by reference to Bartley et al. The Bartley et al. reference does not teach or suggest identifying at least one immunodominant epitope using an antibody or population of antibodies from a naïve human or animal and/or modifying at least one immunodominant epitope. Thus, the cited references in combination do not teach or suggest all of the elements of the claimed invention.

Moreover, as discussed previously with respect to claims 2, 3 and 22, the Bartley et al. reference does not teach or suggest identifying an immunodominant epitope in a polypeptide that has at least 80% sequence identity to an endogenous polypeptide of a human or animal. Nor does this reference identify an immunodominant epitope using an antibody or population of antibodies from a naïve human or animal. Thus, Applicants respectfully request withdrawal of the 35 U.S.C. § 103 rejection on this basis.

#### Summary

Applicants submit the claims are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative if prosecution may be assisted.

Respectfully submitted,

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Minneapolis, Minnesota 55402-0903  
(612) 332-5300

Date: February 5, 2003

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Reg. No. 36,848  
KMK:sab



**MARKED-UP VERSION TO SHOW CHANGES MADE**

2. (Amended) A method according to claim 1 wherein the polypeptide [is a recombinant polypeptide that] has an amino acid sequence that [is homologous to all or a part of a] has at least 80% sequence identity to a full-length native sequence or native sequence lacking a signal sequence or an extracellular domain of an endogenous polypeptide in the human or animal.

3. (Amended) A method according to claim [1] 2, wherein the polypeptide [is a recombinant polypeptide that] has an amino acid sequence [has identical to all or part of a] about 100% sequence identity to a full-length native sequence or native sequence lacking a signal sequence or an extracellular domain of an endogenous polypeptide in the human or animal.

5. (Amended) A method according to claim 1, wherein the animal is selected from the group consisting of[ humans,] primates, cattle , pigs, poultry, and mice.

10. (Amended) A method of modifying a therapeutic polypeptide, comprising:

a) identifying at least one immunodominant epitope [on] in a therapeutic polypeptide, wherein the immunodominant epitope is identified by binding to an antibody or population of antibodies from a naïvehuman or animal and by binding to an antibody or population of antibodies from the human or same species of animal [an animal or human] dosed with the therapeutic polypeptide; and

b) modifying the immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the therapeutic polypeptide.

11. (Amended) A method of modifying a therapeutic polypeptide, comprising:

a) identifying at least one epitope on a therapeutic polypeptide, wherein the epitope binds to an antibody or population of antibodies from a naïve [human or] animal and binds to an antibody or population of antibodies from the human or the same species of animal [an animal or human] dosed with the therapeutic polypeptide;

b) determining whether the epitope is an immunodominant epitope by using the antibody or population of antibodies from a naïve human or animal and by using an antibody or population of antibodies from a human or the same species of animal dosed with the therapeutic polypeptide; and

c) modifying the immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the polypeptide.

13. (Amended) A method of modifying a therapeutic polypeptide, comprising:

a) identifying at least one immunodominant epitope of a therapeutic polypeptide by using an antibody or population of antibodies from a naïve human or animal or population thereof,

b) selecting [the] an immunodominant epitope that is not located in a region of the polypeptide providing a therapeutic activity of the polypeptide; and

c) modifying the selected immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the therapeutic polypeptide.

22. (Amended) A method for selecting at least one immunodominant epitope to be modified in a polypeptide, comprising:

a) identifying at least one epitope in the polypeptide recognized by an antibody or population of antibodies from a naïve human or animal or population thereof and recognized by an antibody or population of antibodies from a human or the same species of animal or population thereof dosed with the polypeptide, wherein the polypeptide [is homologous to] has at least 80% sequence identity to an endogenous polypeptide in the human or the same species of animal; and

b) selecting at least one at least one immunodominant epitope from[of] the identified epitopes by determining whether the identified epitope [is in at least one

immunodominant epitope in the polypeptide]more frequently elicits an antibody response than other epitopes in the polypeptide.

30. (Amended) A method of modifying a nucleic acid encoding a modified polypeptide comprising:

a) identifying at least one immunodominant epitope [~~in the~~in a polypeptide by using an antibody or population of antibodies obtained from a naive human or animal or population thereof;

b) providing an isolated nucleic acid sequence encoding the polypeptide; and

c) modifying the isolated nucleic acid to encode a modified polypeptide wherein the modified polypeptide has at least one change in the immunodominant epitope and wherein the change reduces an immune response to the polypeptide while still retaining a substantial therapeutic activity of the polypeptide.

31. (Amended) [The method according to claim 30, further comprising transforming a] A host cell transformed with the modified isolated nucleic acid of claim 30.



Figure 7

~~-21~~ 1 meltelllv mllltarl<sup>1</sup>tl sspappacdl rvlskllrds hvlhsrlsqc pevhlptpv

~~40~~ 61 lpavdfs<sup>1</sup>lg ewktqmeetk aqdlgavtl l<sup>1</sup>legvmaarg qlgptclssl lgqlsgqvrl

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~~280~~ 301 tgqytlfplp ptlptpvvql hpllpdpsap tptptspln tsythsqnls qeg

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Limits Index History Clipboard

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(ML) (MEGAKARYOCYTE GROWTH AND DEVELOPMENT FACTOR) (MGDF)BLink, PubMed,  
Related Sequences, Taxonomy, OMIM, LinkOut

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annotation updated: Oct 1, 2000.  
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KEYWORDS Cytokine; Glycoprotein; Hormone; Signal; Alternative splicing.  
SOURCE human.  
ORGANISM Homo sapiens  
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;  
Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.  
REFERENCE 1 (residues 1 to 353)  
AUTHORS de Sauvage,F.J., Hass,P.E., Spencer,S.D., Malloy,B.E., Gurney,A.L.,  
Spencer,S.A., Darbonne,W.C., Henzel,W.J., Wong,S.C., Kuang,W.-J.,  
Oles,K.J., Hultgren,B., Solberg,L.A.Jr., Goeddel,D.V. and  
Eaton,D.L.  
TITLE Stimulation of megakaryocytopoiesis and thrombopoiesis by the c-Mpl  
ligand  
JOURNAL Nature 369 (6481), 533-538 (1994)  
MEDLINE 94261202  
REMARK SEQUENCE FROM N.A. (ISOFORM 1).  
TISSUE=Fetal liver  
REFERENCE 2 (residues 1 to 353)  
AUTHORS Bartley,T.D., Bogenberger,J., Hunt,P., Li,Y.-S., Lu,H.S.,  
Martin,F., Chang,M.-S., Samal,B.B., Nichol,J.L., Swift,S.,

Johnson, M.J., Hsu, R.-Y., Parker, V.P., Suggs, S., Skrine, J.D., Merewether, L.A., Clogson, C., Hsu, E., Hokom, M.M., Hornkohl, A., Choi, E., Pangelinan, M., Sun, Y., Mar, V., McNich, J., Simonet, L., Jacobsen, F., Xie, C., Shutter, J., Chute, H., Basu, R., Selander, L., Trollinger, D., Sieu, L., Padilla, D., Trail, G., Elliott, G., Izumi, R., Covey, T., Crouse, J., Garcia, A., Xu, W., del Castillo, J., Biron, J., Cole, S., Hu, M.C.-T., Pacifici, R., Ponting, I., Saris, C., Wen, D., Yung, Y.P., Lin, H. and Bosselman, R.A.

TITLE Identification and cloning of a megakaryocyte growth and development factor that is a ligand for the cytokine receptor Mpl  
JOURNAL Cell 77 (7), 1117-1124 (1994)  
MEDLINE 94291201  
REMARK SEQUENCE FROM N.A. (ISOFORM 1).  
TISSUE=Fetal liver  
REFERENCE 3 (residues 1 to 353)  
AUTHORS Foster, D.C., Sprecher, C.A., Grant, F.J., Kramer, J.M., Kuijper, J.L., Holly, R.D., Whitmore, T.E., Heipel, M.D., Bell, L.A.N., Ching, A.F., McGrane, V., Hart, C., O'Hara, P.J. and Lok, S.  
TITLE Human thrombopoietin: gene structure, cDNA sequence, expression, and chromosomal localization  
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 91 (26), 13023-13027 (1994)  
MEDLINE 95108091  
REMARK SEQUENCE FROM N.A. (ISOFORM 1).  
REFERENCE 4 (residues 1 to 353)  
AUTHORS Sohma, Y., Akahori, H., Seki, N., Hori, T., Ogami, K., Kato, T., Shimada, Y., Kawamura, K. and Miyazaki, H.  
TITLE Molecular cloning and chromosomal localization of the human thrombopoietin gene  
JOURNAL FEBS Lett. 353 (1), 57-61 (1994)  
MEDLINE 95010765  
REMARK SEQUENCE FROM N.A. (ISOFORM 1).  
REFERENCE 5 (residues 1 to 353)  
AUTHORS Gurney, A.L., Kuang, W.J., Xie, M.H., Malloy, B.E., Eaton, D.L. and de Sauvage, F.J.  
TITLE Genomic structure, chromosomal localization, and conserved alternative splice forms of thrombopoietin  
JOURNAL Blood 85 (4), 981-988 (1995)  
MEDLINE 95152076  
REMARK SEQUENCE FROM N.A. (ISOFORMS 1 AND 2).  
REFERENCE 6 (residues 1 to 353)  
AUTHORS Kato, T., Ogami, K., Shimada, Y., Iwamatsu, A., Sohma, Y., Akahori, H., Horie, K., Kokubo, A., Kudo, Y., Maeda, E., Kobayashi, K., Ohashi, H., Ozawa, T., Inoue, H., Kawamura, K. and Miyazaki, H.  
TITLE Purification and characterization of thrombopoietin  
JOURNAL J. Biochem. 118 (1), 229-236 (1995)  
MEDLINE 96015174  
REMARK SEQUENCE FROM N.A. (ISOFORM 1).  
TISSUE=Liver  
REFERENCE 7 (residues 1 to 353)  
AUTHORS Chang, M., McNinch, J., Basu, R., Shutter, J., Hsu, R., Perkins, C., Mar, V., Suggs, S., Welcher, A., Li, L., Lu, H., Bartley, T., Hunt, P., Martin, F., Samal, B. and Bogenberger, J.  
TITLE Cloning and characterization of the human megakaryocyte growth and development factor (MGDF) gene  
JOURNAL J. Biol. Chem. 270 (2), 511-514 (1995)  
MEDLINE 95122483  
REMARK SEQUENCE FROM N.A. (ISOFORM 1).

REFERENCE TISSUE=Placenta  
 8 (residues 1 to 353)  
 AUTHORS Im,S.H., Lee,W.S. and Chung,K.H.  
 TITLE Direct Submission  
 JOURNAL Submitted (??-MAY-1996) to the EMBL/GenBank/DDBJ databases  
 REMARK SEQUENCE FROM N.A. (ISOFORMS 1 AND 3).  
 COMMENT

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 This SWISS-PROT entry is copyright. It is produced through a  
 collaboration between the Swiss Institute of Bioinformatics and  
 the EMBL outstation - the European Bioinformatics Institute.  
 The original entry is available from <http://www.expasy.ch/sprot>  
 and <http://www.ebi.ac.uk/sprot>  
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 [SIMILARITY] BELONGS TO THE EPO / TPO FAMILY.  
 [DATABASE] NAME=R&D Systems' cytokine source book;  
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241 dqipgyl nri hellngtrgl fpgpsrrtlg apdissgtsd tgs lppnlqp gyspspthpp
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